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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,428	07/10/2002	Ian Georges Charles	HO-P02380USO	3647

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EXAMINER	
GARVEY, TARA L	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,428	CHARLES ET AL.	
	Examiner	Art Unit	
	Tara L. Garvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 52-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 52-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 July 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Claims 1 and 52-58 are pending. Receipt is acknowledged of an amendment filed on March 6, 2006 in which claims 3-4, 6-24, 34-42 and 46-50 were canceled and new claims 52-58 were added.

Election/Restrictions

Applicant's election of Group I in the reply filed on March 6, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

In the specification, sequences are present on page 11, line 16, page 36, line 2 and page 40, line 30, which do not have sequence identifiers. See attached Notice to Comply.

In response to this office action, Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). The nature of the non-

compliance did not preclude an examination of the elected invention on the merits, the results of which are presented below.

Priority

The reference to the priority application PCT/GB00/02932 does not appear in the first paragraph of the specification. Please amend the first paragraph of the specification to recite that this application is a 371 of PCT/GB00/02932 filed on July 28, 2000.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 52-58 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. A cell can contain a construct in which a promoter is operably linked to tetracycline operator sequences and a coding sequence for nitric oxide synthase (NOS). The step where the cell is treated with tetracycline to induce the expression of the NOS is omitted in the claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 52-55, 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morris, BJ (Journal of Biological Chemistry (1995) volume 270(42), pages 24740-24744) in view of Cerasoli, F (WO 98/26066).

Claim 1 is drawn to a method of identifying NO-modulated polynucleotides comprising providing an mRNA or cDNA population from cells which comprise a NOS coding sequence operably linked to an ecdysone-responsive promoter or a tetracycline regulated promoter, inducing the expression of the NOS in the cells and comparing the expression of mRNA or cDNA from the uninduced and induced cells to determine the effect of NO on the expression of polynucleotides. Claims 52-55 further limit the invention to a specific NOS such as inducible NOS, endothelial NOS or neuronal NOS. Claims 57 and 58 further limit the invention to the polynucleotide construct being a vector and being comprised in a cell.

Morris, BJ teaches a method of identifying a nitric oxide regulated polynucleotide that comprises exposing primary cultures of striatal neurons to NO-releasing agents and analyzing the cells for the expression of mRNA levels for *c-fos* and *zif/268* using in situ hybridization and northern blot analysis. The determination of the increase in the level of *c-fos* and *zif/268* mRNA in the treated cells was made by comparison with a control group of cells not exposed to a NO-inducing agent (abstract, page 24740, right column to page 24741, top of right column, page 24741, right column last paragraph, page 24743, Table II).

Morris does not teach using an inducible expression vector that uses an ecdysone responsive promoter or a promoter linked to *tet* operator sequences to express the coding sequence for a NOS and result in the production of NO in the cells.

Cerasoli, F teaches genetically engineering cells in order to permit the regulated expression of NO synthase (page 3, lines 2-5). In particular, Cerasoli, F teaches a vector that encodes a nitric oxide synthase (e.g. inducible NOS, endothelial NOS or neuronal NOS) and the expression of the NOS is controlled by an ecdysone responsive promoter or a promoter linked to the bacterial *tet* operon. The vector is introduced into to cells and the expression of the NOS is induced by administering ecdysone or muristerone to the cells for the ecdysone responsive promoter or tetracycline or doxycycline for the promoter linked to *tet* operator sequences (page 3 to page 4, line 15, page 6, lines 1-19, page 11, line 22 to page 12, line 22, page 16, lines 17-20, page41, lines 9-18 and page 54-57). The ecdysone responsive promoter taught in the reference comprises ecdysone responsive elements (EcRE) and a minimal promoter

such as that derived from the Drosophila heat shock promoter as evidence by (No et al. PNAS (1996) volume 93, pages 3346-3351, see page 3346, right column, first full paragraph and page 3347, Figure 2).

It would have been obvious to one of ordinary skill in the art to modify the teachings of Morris, BJ to produce NO within the cells using an ecdysone or tetracycline inducible promoter system to express sequences coding NOS because Morris, BJ teach that it is within the ordinary skill in the art to determine the effect of NO produced in a cell on the expression of a polynucleotide and because Cerasoli, F demonstrate that NO can be produced in a cell by introduction of a construct into cells that encodes a NOS such as iNOS, eNOS or nNOS under the control of inducible promoter such as an ecdysone responsive promoter or a *tet* regulated promoter. One would have been motivated to do so in order to receive the expected benefit, as suggested by Cerasoli, F, of being able to produce NO in a cell at desired time and for a desired time period. Absent of any evidence to the contrary, there would have been reasonable expectation of success in using the inducible expression system taught by Cerasoli, F in the method of analyzing the modulated expression of genes induced by NO taught by Morris, BJ.

Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Morris, BJ (Journal of Biological Chemistry (1995) volume 270(42), pages 24740-24744) in view of Cerasoli, F (WO 98/26066) and in further view of Gossen et al (PNAS (1992) volume 89, pages 5547-5551).

Claims 1, 52-55, 47 and 58 have been described previously. Claim 56 further limits the invention to the promoter being operably linked to two *tet* operator sequences.

Morris, BJ and Cerasoli, F have been described previously.

Morris, BJ and Cerasoli, F do not teach that the promoter is operably linked to two *tet* operator sequences.

Gossen et al teaches that gene expression in mammalian cells can be controlled by tetracycline-responsive promoters that contain two *tet* operator sequences (page 5548, left column, second paragraph bridging right column and page 5549, left column, second full paragraph to right column first paragraph).

It would have been obvious to one of ordinary skill in the art to modify the combined teachings of Morris, BJ and Cerasoli, F to use a construct for the regulatable expression of NOS in cells that contains two *tet* operator sequences operably linked to the promoter because Morris, BJ and Cerasoli, F teach that it is within the ordinary skill in the art to determine the effect of NO produced in a cell on the expression of a polynucleotide in which NOS is expressed from tetracycline inducible promoter system and because Gossen et al demonstrate that tetracycline induceible promoters can contain two *tet* operator sequences. One would have been motivated to do so in order to receive the expected benefit, as suggested by Gossen et al, of being able regulate the expression of NOS under a tightly controlled system. Absent of any evidence to the contrary, there would have been reasonable expectation of success in using the tetracycline promoter system containing two *tet* operators taught by Gossen et al in the

method of analyzing the modulated expression of genes induced by NO taught by the combined teachings of Morris, BJ and Cerasoli, F.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tara L Garvey whose telephone number is (571) 272-2917. The examiner can normally be reached on Monday through Friday 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) (http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tara L Garvey, Ph.D.
Examiner
Art Unit 1636

TLG

CELINE QIAN, PH.D.
PRIMARY EXAMINER

Notice to Comply	Application No. 10/049,428	Applicant(s) Charles et al	
	Examiner Tara L. Garvey	Art Unit 1636	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: In the specification, sequences are present on page 11, line 16, page 36, line 2 and page 40, line 30, which do not have sequence identifiers

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the specification**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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